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Platelet microparticles: a new player in cerebral malaria pathogenesis

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One of the known mechanisms of cerebral malaria (CM) is the sequestration, within brain microvessels, of *Plasmodium falciparum*-parasitized red blood cells (PRBC), but also of leucocytes and platelets. Besides, CM is characterized by an overproduction of pro-inflammatory cytokines, inducing endothelial activation. This activation notably leads to the overexpression of adhesion molecules and to the release of microparticles, derived from various cell types within the vascular compartment. Microparticles are submicronic membranous elements carrying on their surface proteins from their cell of origin, which bestow on them specific biological properties. Because platelet-derived microparticles (PMP) represent the majority of circulating microparticles and because platelets have been shown to modulate PRBC cytoadherence, we analyzed the potential role of PMP in this cytoadherence.

To this aim, we used an *in vitro* model of human CM involving co-cultures of PMP, purified from A23187-activated platelets, enriched late-trophozoïte PRBC from the IP-PAM strain, and the human brain microvascular endothelial cell line HBEC-5i.

We demonstrated by confocal microscopy and flow cytometry that PMP both bound to and were internalized by HBEC-5i, and as a consequence enhanced the expression of adhesion receptors involved in CM pathogenesis, such as ICAM-1 and VCAM-1. Furthermore, we showed that PMP were able to bind to PRBC thereby transferring platelet antigens to PRBC surface. PMP binding to PRBC was not affected by temperature or phosphatidylserine blockade by annexin V but was significantly reduced when PRBC were treated with trypsin or when PRBC were incubated with PMP in the presence of antibodies against platelet CD31 (PECAM-1) and CD36 (GPIV). Lastly, PMP, while interacting with the two other cell types, dramatically increased PRBC cytoadherence to both resting and TNF-prestimulated HBEC-5i.

PMP thus appear to be an important element in RBC sequestration and in endothelial pathology, raising a novel mechanism by which PMP may participate in CM pathogenesis.